Translation

PCT/JP2003/011847

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PF-030009-WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP2003/011847	International filing date (*day/month/year*) 17 September 2003 (17.09.2003)	Priority date (*day/month/year*)
International Patent Classification (IPC) or national classification and IPC A61K 45/00, 31/51, A61P 3/10		
Applicant KAWASUGI, Kaname		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31 March 2005 (31.03.2005)	28 November 2005 (28.11.2005)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP2003/011847

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☐ the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the claims:

pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP 03/11847

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-8	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-8	NO
Industrial applicability (IA)	Claims	1-8	YES
	Claims		NO

2. Citations and explanations

The following documents are cited in the international search report.

Document 1: WO 02/51441 A1 (Sankyo Co., Ltd.)

Document 2: Hiroshi TAMAI, "Tonyobyo to Vitamin," Japanese Journal of Clinical Medicine, Vol. 57, No. 10, 1999, pages 200 to 203

Document 3: Naotaka HASHIZUME, "Vitamin B1 Ketsubosho," Igaku no Ayumi, Vol. 198, No. 13, 2001, pages 949 to 952

Document 4: US 3502674 A (Shionogi and Co., Ltd.)

Claims 1 to 7

Document 1 discloses medicinal compositions which comprise an insulin resistance-improving drug that ~~exhibits~~ an agonist activity against the peroxisome proliferator activated receptor γ.

Therein, document 1 further indicates that the abovementioned insulin resistance-improving drug causes side effects such as edemas and heart enlargement, and that it is possible to include medicaments for preventing the side effects in question within the medicinal compositions.

Meanwhile, document 2 indicates that in diabetics, sustained high blood sugar levels cause the consumption of vitamin B1, which can in turn lead to a relative deficiency of vitamin B1 *in vivo*; therein, document 2 also suggests the administration of vitamin B1 to diabetics in order to remedy this vitamin B1 deficiency.

Therefore, it would have been obvious to a person skilled in the art of the technical field in question to administer vitamin B1, which is known to be deficient in diabetics, in combination with the medicinal compositions that comprise insulin resistance-improving drugs, which are administered to diabetics.

Furthermore, the effects that result from the configuration in question cannot be considered to be significant.

In the written response, the applicant asserts that although it is known that diabetics suffer from a relative deficiency of vitamin B1 *in vivo*, this deficiency is rarely considered to be sufficient to cause the symptoms of a vitamin B1 deficiency in diabetics who are not using an insulin resistance-improving drug that exhibits an agonist activity against the peroxisome proliferator activated receptor γ; asserts that hypothetically, even if said deficiency were sufficient to cause deficiency symptoms, said symptoms would for the most part be confined to Wernicke encephalitis, peripheral nervous system disorders or the like, and would rarely include symptoms such as edemas (e. g. wet beriberi) or heart enlargement; and asserts that as a result, there is no reason to hastily presume that a vitamin B1 deficiency is the cause of symptoms such as edemas or heart enlargement, which are characteristic in diabetics to whom an insulin resistance-improving drug that exhibits an agonist activity against the peroxisome proliferator activated receptor γ is being administered, in the light of the

disclosures of document 2. Indeed, it truly is unclear whether or not symptoms such as edemas or heart enlargement, which are characteristic in diabetics to whom an insulin resistance-improving drug that exhibits an agonist activity against the peroxisome proliferator activated receptor γ is being administered, are being caused by a vitamin B1 deficiency. However, the applicant acknowledges that diabetics suffer from a relative deficiency of vitamin B1 *in vivo*; document 2 suggests the active administration of vitamins in order to ameliorate vitamin deficiencies that occur as the secondary symptoms of a disorder and to prevent the complications that can arise therefrom; and it is common practice to supplement a medicinal composition with well-known components that exhibit a therapeutic effect in relation to any of the various conditions that are caused by a primary disease. Therefore, it would have been obvious to a person skilled in the art of the technical field in question to add a vitamin B1 supplement in order to combat vitamin B1 deficiencies in diabetics, who are known to exhibit such deficiencies.

Claim 8

Document 3 indicates that vitamin B1 deficiencies cause edemas and heart enlargement.

Meanwhile, document 4 indicates that the administration of vitamin B1 derivatives is useful for ameliorating the symptoms that are caused by vitamin B1 deficiencies, such as edemas.

The invention that is set forth in the abovementioned claim prevents side effects such as edemas or heart enlargement. However, document 1 indicates that insulin resistance-improving drugs which exhibit an agonist activity against the peroxisome proliferator activated receptor γ cause side effects such as edemas and

heart enlargement, and the fact that vitamin B1 exhibits an action whereby it ameliorates the symptoms in question was well know prior to the priority date of the present international application, as disclosed in documents 3 and 4; therefore, even if it is unclear whether or not symptoms such as edemas or heart enlargement, which are characteristic in diabetics to whom an insulin resistance-improving drug that exhibits an agonist activity against the peroxisome proliferator activated receptor γ is being administered, are being caused by a vitamin B1 deficiency, it would have still been obvious to a person skilled in the art of the technical field in question to employ a combination of the medicinal composition and vitamin B1 with the expectation of achieving an ameliorating action in relation to the symptoms in question, and to confirm the results that are obtained by means of such a configuration.

As a result, the inventions that are set forth in the abovementioned claims lack novelty and do not involve an inventive step in the light of documents 1 to 4.